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Original article

Body mass index and susceptibility to knee osteoarthritis: A systematic review and meta-analysis

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ABSTRACT

Objective: Excess bodyweight, expressed as increased body mass index, is associated with osteoarthritis risk, especially in weight bearing joints. However, the strength of the association was inconsistent. The study was conducted to quantitatively assess the association between body mass index and the risk of knee osteoarthritis and investigate the difference of the strength stratified by sex, study type and osteoarthritis definition.

Methods: We used published guidelines of the Meta-analysis of Observational Studies in Epidemiology Group (MOOSE) to perform the meta-analysis. The search strategy employed included computerized bibliographic searches of MEDLINE, PubMed, EMBASE, The Cochran Library and references of published manuscripts. Study-specific incremental estimates were standardized to determine the risk of knee osteoarthritis associated with a 5 kg/m^2 increase in BMI.

Results: Twenty-one studies were included in the study. The results showed that body mass index was significantly positive associated with osteoarthritis risk in knee site. A 5-unit increase in body mass index was associated with an 35% increased risk of knee osteoarthritis (RR: 1.35; 95%CI: 1.21, 1.51). Magnitude of the association was significantly stronger in women than that in men with significant difference (men, RR: 1.22; 95%CI: 1.19, 1.25; women, RR: 1.38; 95%CI: 1.23, 1.54; $p = 0.04$). The summary effect size was 1.25(95%CI: 1.18, 1.32) in case-control studies and 1.37 (95%CI: 1.19, 1.56) in cohort studies ($p = 0.28$). Body mass index was positively associated with knee osteoarthritis defined by radiography and/or clinical symptom (RR: 1.25, 95%CI: 1.17, 1.35) and clinical surgery (RR: 1.54, 95%CI: 1.29, 1.83). The latter tended to be stronger than the former ($p < 0.01$).

Conclusion: Increased body mass index contribute to a substantially increased risk of knee OA. The magnitude of the association varies by sex and OA definition.

1. Introduction

Osteoarthritis (OA) is the most common joint disease and is one of the most prevalent symptomatic health problems for older individuals. The etiology of OA is multifactorial, including inflammatory factors, metabolic factors, and mechanical factors [1]. OA have incurred substantial disease burden and influenced the quality of daily life for the elderly. Knee joint is the most clinically affected site, and knee OA is the main indication for a large number of knee replacement surgeries performed annually [2].

Obesity has become a global problem leading to excess morbidity and mortality. According to the latest World Health Organization (WHO) report, more than 1.6 billion adults (aged 15 years old) are overweight [3]. Obesity has drawn interest in recent studies because of its modifiable status and its association with OA. There is considerable evidence indicating that obesity plausibly represents one of the most important risk factors for particular peripheral joint sites, predominantly the knee site and the hip site [4–11].

Standard therapeutic modalities can alleviate symptoms and improve function but cannot alter the disease process [10]. Therefore, much attention has been invested in improving the recognition of epidemiology and in elucidating possible factors predisposing to OA development. Mechanical stress resulting from a high body mass index (BMI) is known to be a risk factor for the development of knee OA, and better understanding of the positive effect of obesity on OA development is likely to be valuable in the

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campaign against osteoarthritis. To our knowledge, many epidemiologic studies have been performed to investigate the association between obesity with knee OA, and obesity is an unequivocal risk factor for the onset and progression of knee OA [9,12,13]. However, the link between obesity and the risk of knee OA lack quantitatively assessment.

It is probable that once sufficient information is provided through systematic studies, we will be able to obtain a better understanding of the cause of OA as a whole and perhaps develop new interventions to lower the prevalence of obesity and knee OA in the future. Therefore, we conducted a meta-analysis and meta-regression to quantitatively clarify the association between BMI, as a measure of overall obesity, and the risk of developing knee OA based on available studies to date.

2. Methods

2.1. Search strategy and inclusion criteria

The search strategy included computerized bibliographic searches of PubMed (1966–2010), EMBASE (1974–2010) and references of published manuscripts. The Cochrane Library of Systematic Reviews also was queried. Other websites searched included National Institute for Clinical Excellence, National Electronic Library for Health- musculoskeletal specialist library, Arthritis Research Campaign, Arthritis Care, Arthritis and Musculoskeletal Alliance, and Arthritis Foundation National Office. The search terms included obesity, overweight, BMI, adiposity, arthritis, osteoarthritis and OA. Studies in humans of the association between BMI and knee OA were included if they met the following criteria:

- the study was English-language articles;
- the study was of a cohort, or a (nested) case-control study reported the association with corresponding confidence intervals (95%CI) for at least three categories of exposure (BMI), or must provide sufficient data to estimate them. Height and weight or BMI must be provided in those studies;
- the study was on primary or idiopathic knee OA, while not secondary OA
- the study was on the relationship between obesity and knee joint replacements.

No specific limits of ethnicity, the type of knee OA (femorotibial and patello-femoral OA), and the site of knee OA (unilateral or bilateral knee OA) were set.

The titles and abstracts were scanned to exclude studies that were clearly irrelevant. The full texts of the remaining articles were read to determine whether they contained information about our interest. In addition, the electronic searches were supplemented by scanning reference lists from retrieved articles to identify additional studies. For studies with same population resources or over-lapping datasets, the most complete one was included. The excluded studies included reviews, conference abstracts, letters to editors and studies on the progression of OA.

2.2. Data extraction and quality assessment

Data were extracted using a standardized data extraction form and the information of studies was assessed by two investigators independently. Discrepancies were resolved by discussion and repeated examination of the included articles The following information was used for each study: The first author's name, year of publication, country where the study was performed, participant population, study design, OA definition/assessment, risk estimates with corresponding 95%CI either with one BMI category as the reference or expressed as a slope per incremental BMI, covariates controlled in the study.

For measuring quality of observational studies no universal scale was available, therefore, we followed the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group and assessed the quality of the included studies based on the following criteria [14]:

- clear description of the population and setting;
- sufficient sample size;
- appropriate measurement of outcomes;
- response rate of the original study was higher than 80%;
- completeness of follow-up or questionnaires;
- appropriate consideration and adjustment for potential confounders;
- knee OA was assessed identical in studied population;
- exposure was measured identical for cases and controls;
- information on completers vs. withdrawals;
- exact statistical and analytical methods.

Throughout this assessment, when information about a specific item was consistent with the criteria, it was scored as "1"; otherwise, it was scored as "0". Studies that fulfilled more than eight criteria were considered high quality (i.e., scored ≥ 8).

2.3. Statistical analysis

Meta-analysis was performed for each individual study using Stata 8.0 (Stata Corp, College Station, TX). Briefly, the analysis software produced forrest plots as a schematic description of the meta-analysis results. Summary random effect estimates were reported using pooled odds ratios (OR), and 95% confidence intervals (CI) that were calculated around each summary effect estimate. The random effect model assumed that included study was a random sample of a hypothetical population of study.

Study-specific OR and corresponding 95%CI was chosen rather than weight to explore the association because of the wide variation in average weight and height across races. The cut-off for exposure categories varied between studies included in the study. In order to keep all studies on a coincident scale, category-specific risk was transformed into risk estimates associated with per 5 kg/m^2 increments in BMI for each study instead of per 1 kg/m^2 increment, which would be impractical and non-significant. Therefore, for practical reasons per 5 kg/m^2 increments in BMI has been used as a surrogate for the change of bodyweight. These estimates were calculated on the assumption of a linear trend between the natural logarithm of OR and increased BMI for different exposure category [15]. Scaled OR was estimated using the method described by Greenland [16]. As most studies have reported effect size and their corresponding 95%CI, we used these data as summary statistics for each study. The value assigned to each BMI category was the mid-point for closed categories. For open-ended categories (e.g., BMI > 30), we estimated the median (assuming a normal distribution for BMI) [17]. Unless special statement, the adjusted risk estimate from each study was used.

Heterogeneity testing using Q statistics was performed to evaluate variance between studies [18]. If the between-study variance was large enough to make the test of heterogeneity significant ($P < 0.05$), random effects models were considered most appropriate. As these tests of heterogeneity were relatively insensitive, a more conservative P-value of less than 0.10 was used. Finally, the potential publication bias was examined with funnel plots, which plot the log of effect sizes against the inverse standard error of the effect size. The Egger's regression test was used to test funnel plot asymmetry [19]. A P-value < 0.05 was considered significant for publication bias. We also conducted sensitivity analysis omitting

each study to assess whether result was influenced excessively by a single study [20].

3. Results

3.1. Studies included in the meta-analysis

The primary literature search had identified 414 potentially relevant studies. After review of these titles and abstracts, we retrieved full articles for further assessment. A total of 44 studies have been identified. Twenty-three studies were excluded for unavailable or incomplete data [7,21–42]. Finally, 21 unique studies were available for this meta-analysis, including 15 cohort studies [9,11–13,43–53] and six case-control studies [54–59]. The number of included studies whose definition of OA was based on clinical surgery was six studies [13,46,50,55,57,59], on radiography seven studies [11,12,45,48,51,53,58], on radiography and clinical symptom six studies [9,43,44,52,54,56], and on self-reported two studies [47,49]. Fig. 1 shows the search and selection process. Table 1 summarizes the characteristics of included studies.

3.2. Meta-analysis of increased BMI and the risk of knee OA

The analysis involved 872 717 subjects from 18 studies. A summary of meta-analysis for the association between obesity and susceptibility to knee OA was shown in Fig. 2. A 5-unit increase in BMI was significantly related to an increased risk of knee OA (RR: 1.35; 95%CI: 1.21, 1.51; $P < 0.001$ for Q test; $I^2 = 99.20\%$ for heterogeneity). This suggested that every 5-unit increase in BMI was associated with a 35% increased risk of knee OA.

We also carried subgroup analysis to examine whether the association was different because of stratification by sex, study design and definition of knee OA. For different sex, the association was 1.38(95% CI: 1.23–1.54; $P < 0.001$ for Q test; $I^2 = 97.00\%$ for heterogeneity) in women and 1.22 (95%CI: 1.19, 1.25; $P = 0.71$ for Q test; $I^2 < 0.001\%$ for heterogeneity) in men with significant difference ($P = 0.04$) (Table 2). Examined case-control studies and cohort studies separately, we found that the summary association was 1.25(95%CI: 1.18, 1.32; $P = 0.15$ for Q test; $I^2 = 44.40\%$ for heterogeneity) in case-control studies and 1.37 (95%CI: 1.19, 1.56; $P < 0.001$ for Q test; $I^2 = 99.40\%$ for heterogeneity) in cohort studies with no statistical significant difference ($P = 0.28$) (Table 2). To assess the association in more details, we further conducted the analysis according to the definition of OA (clinical surgery versus clinical symptom or radiography or clinical symptom + radiography). The end-point was precisely categorized into non-clinical surgery (radiography and/or clinical symptom) and clinical surgery. The association was 1.25(95%CI: 1.17, 1.35; $P < 0.001$ for Q test; $I^2 = 93.20\%$ for heterogeneity) defined by radiography and/or clinical symptom and 1.54(95%CI: 1.29, 1.83; $P < 0.001$ for Q test; $I^2 = 98.60\%$ for heterogeneity) defined by clinical surgery, respectively. The latter tended to give larger effect than the former ($P < 0.01$) (Table 2).

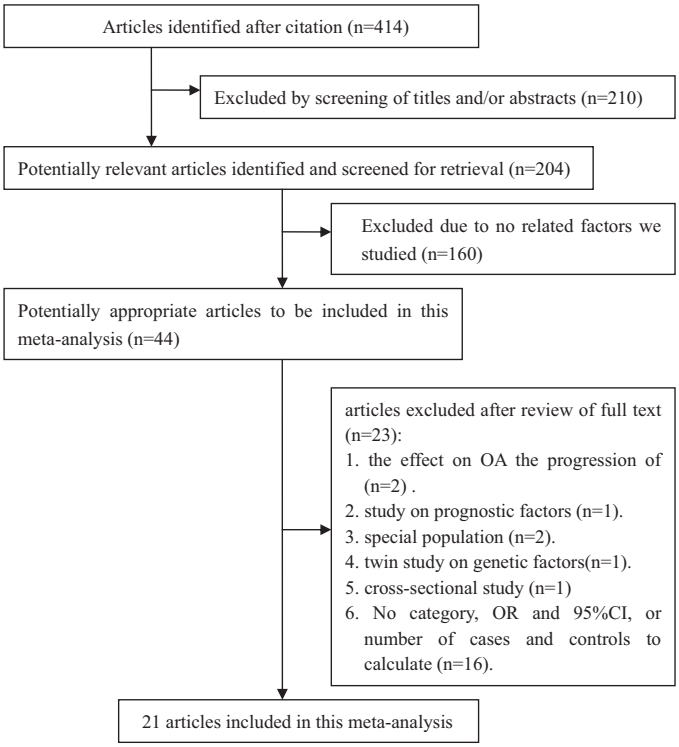

Fig. 1. Flow chart of article selection.

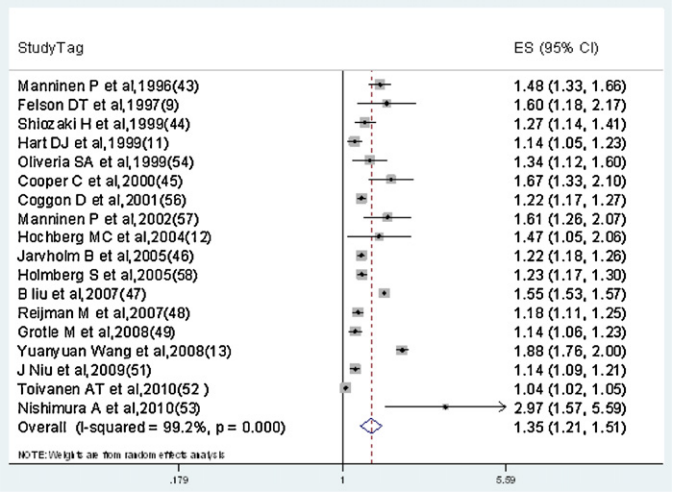

Fig. 2. The forest plot of the association between BMI and knee OA using random-effects model.

3.3. Heterogeneity and publication bias

Significant heterogeneity between studies was noted in cohort studies, while moderate heterogeneity in case-control studies. It was difficult to correlate the funnel plot, which is usually used to detect publication bias, because the number of studies included in the analysis was relatively small. No publication bias was detected by Egger's regression ($P = 0.95$), but Begger methods had tested bias opposing to Egger's regression ($P = 0.03$). Trim and fill analysis showed no study might have been missing. Influence analysis produced similar summary risk estimates and did not affect the strength of evidence for increased BMI and the risk of knee OA.

4. Discussion

The meta-analysis shows that the risk of knee OA increase with BMI and a dose-response relationship exist. A 5-unit increase in BMI is significantly associated with an increased risk of developing knee OA (RR: 1.35; 95%CI: 1.21, 1.51). That is, every 5-unit increase in BMI is associated with a 35% increased risk of knee OA. Our findings support the notion that there is a positive association between increased BMI and the risk of knee OA. Meanwhile, our results provide a quantitative risk estimates and a continuous scale that is a reliably steady result. BMI is analyzed on the continuous scale, and

Table 1
Characteristics of studies on obesity and knee osteoarthritis risk.

Author, year (ref.)	Country	Study participants (% of women)	Study design	Quality of study	No. cases	Mean age of patients (SD)	Definition	OA site	Adjustments
Hart et al., 1999 [11]	England	1003 women aged 49–60 (100)	Prospective cohort study	9	95	55.30 (5.60)	Radiography[a]	Knee	Social classic, smoking, ERT, hysterectomy, knee pain, physical activity
Coggon et al., 2001 [56]	England	1050 men and women aged ≥ 45 (60.95)	Case control study	8	525	NA	Radiography and clinical diagnosis[b]	Knee	Age, gender
Grotle et al., 2008 [49]	Norway	1675 men and women aged 24–66 (56.30)	Prospective cohort study	9	114	NA	Self-reported (based on clinical diagnosis)	Knee	Age, gender, work, leisure time activities
Cooper et al., 2000[45]	England	354 men and women aged ≥ 55 (72.03)	Prospective cohort study	9	45	NA	Radiography[c]	Knee	Age, gender, knee pain
Reijman et al., 2007 [48]	Netherlands	1372 men and women aged ≥ 55 (5.5)	Prospective cohort study	9	76	66.30 (6.70)	Radiography[c]	Knee	Age, gender
Sandmark et al., 1999 [55]	Sweden	1173 men and women aged 55–70 (49.79)	Case control study	8	625	NA	Clinical surgery[d]	TKR	Smoking, hormones, physical loads, housework, sports activities
Jarvholm et al., 2005 [46]	Sweden	320192 men aged 15–67 (0)	Prospective cohort study	9	502	NA	Clinical surgery[d]	TKR	Age, smoking
Oliveria et al., 1999 [54]	Unites states	268 women aged 20–89 (100)	Case control study	8	134	60.8	Radiography and diagnosis[e]	Knee	Estrogen use, smoking, health care
Niu et al., 2009 [51]	United states	2623 men and women aged 54–70 (59.40)	Prospective cohort study	9	163	NA	Radiography[c]	Knee	Age, gender, race, bone mineral density, knee injury
Liu et al., 2007 [47]	England	490532 women aged 50–69 (100)	Prospective cohort study	9	974	NA	Self-reported (based on clinical surgery)	TKR	Age, region of recruitment, deprivation index
Holmberg et al., 2005 [58]	Sweden	1650 men and women aged 51–70 (57.20)	Case control study	8	825	NA	Radiography[c]	Knee	Heredity, knee injury, smoking, sports activity
Wang et al., 2009 [13]	Australia	41528 men and women aged 25–75 (58.95)	Prospective cohort study	9	541	60.30 (6.80)	Clinically surgery[d]	TKR	Age, gender, country of birth, education
Felson et al., 1997 [9]	United states	217men and 381women (63.71)	Prospective cohort study	9	93	NA	Radiography and diagnosis[c]	Knee	Age, gender, smoking, physical activity, knee injury, weight change
Hochberg et al., 2004 [12]	United states	298 men and 139 women aged ≥ 20 (31.81)	Prospective cohort study	9	NA	NA	Radiography[c]	Knee	Age, gender, smoking
Franklin et al., 2009 [59]	Sweden	2576 men and women aged 63–92 (57.10)	Case control study	8	431	73.70	Clinical surgery[d]	TKR	Age, occupation
Lohmander et al., 2009 [50]	Sweden	11026 men and 16934 women aged 45–73 (60.57)	Prospective cohort study	9	471	NA	Clinical surgery[d]	TKA	Age, gender, smoking, physical activity
Manninen et al., 1996 [43]	Finland	6647 men and women aged 40–64 (54.10)	Prospective cohort study	9	126	NA	Radiography and diagnosis[c]	Knee	
Manninen et al., 2002 [57]	Finland	805 men and women aged 55–75 (75.78)	Case control study	8	281	68.87	Clinical surgery[d]	TKR	Age, gender
Shiozaki et al., 1999 [44]	Japan	1191 women aged 40–65 (100)	Prospective cohort study	9	NA	NA	Radiography and diagnosis[c]	Knee	Physical exercise, knee injury
Toivanen AT et al., 2010 [52]	Finland	8000 men and women aged ≥ 30 (54.54)	Prospective cohort study	9	94	NA	Radiography and diagnosis[c]	Knee	Age, gender
Nishimura A et al., 2010 [53]	Japan	261 men and women aged ≥ 65 (63.22)	Prospective cohort study	9	57	70.80 (20.40)	Radiography[c]	Knee	Age, gender, BMI, knee pain, osteoporosis, Heberden's nodes

TKR: total knee replacement; TKA: knee arthroplasty due to osteoarthritis; NA: no available

[a] Radiography: Kellgren and Lawrence index of grade ≥ 1.

[b] Listed for total anthropathy.

[c] Radiography: Kellgren and Lawrence index of grade ≥ 2.

[d] The first clinical surgery for primary osteoarthritis.

[e] Radiography-based definition suggested by the American College of Rheumatology.

Table 2
Summary effect sizes of knee osteoarthritis per 5-unit increase in BMI by sex, study type and OA definition.

Subgroup	No. of studies	Odds ratios (95%CI)	Heterogeneity	
			p for Q test	I^2 (%)
Female	10	1.38 (1.23–1.54)	<0.001	97.00
Male	7	1.22 (1.19–1.25)	0.71	<0.001
Case control study	4	1.25 (1.18–1.32)	0.15	44.40
Cohort study	14	1.37 (1.19–1.56)	<0.001	99.40
Subtotal	18	1.35 (1.21–1.51)	<0.001	99.20
Surgery	4	1.54 (1.29–1.83)	<0.001	98.60
No surgery	14	1.25 (1.17–1.35)	<0.001	93.20
Subtotal	18	1.35 (1.21–1.51)	<0.001	99.20

effect size is converted to be per five units to reflect both overweight BMI of 27 against normal BMI of 22 and obese BMI of 32 against overweight BMI of 27. It is also possible that any point of categories for BMI among normal distribution of population can interpret the increased risk of knee OA. And, the magnitude of the association was slightly stronger in women than men with significant difference in our meta-analysis. A meta-analysis evaluated data on the relationship between obesity and the risk of knee OA [60]. However, the report provided no obvious evidence as a continuous scale for risk estimates of knee OA. Compared to Blagojevic's published meta-analysis on observational studies, we used strict diagnostic criteria for knee OA in order to determine true association between the exposure and the outcome, and provided an obvious evidence of dose-response relationship as a continuous scale.

Meta-analysis of observational studies are prone to bias, and confounding factors that are inherent in original studies brought about different extent of bias. Case control studies are more prone to recall bias such as recalling BMI. In case-control studies patients with symptomatic knee OA might exaggerate the risk of developing OA associated with prior weight because they are more likely to overestimate earlier body weight. We thus restricted our analysis to cohort studies and case control studies separately. However, the magnitude of the association remained similar after being stratified by different study type. This indicated that there was few recall bias.

OA is generally diagnosed by radiography and clinical symptom. Radiographic OA is defined by X-ray based on traditional criteria of Kellgren-Lawrence scales (graded 0–4, where 0 = none; 1 = possible osteophytes only; 2 = definite osteophytes and possible joint space narrowing; 3 = moderate osteophytes and/or definite joint space narrowing; and 4 = large osteophytes, severe joint space narrowing, and/or bony sclerosis). Clinical OA (Symptomatic OA) is diagnosed on the basis of disease histories, symptoms and clinical findings according to standard criteria evaluated by specially trained physicians. The validity of study depends on the accuracy of case definition, which may be one of the reasons that risk estimates are different across studies. In fact, OA is difficult to assess because it combines both symptoms and pathologic changes, the latter is usually recognized by radiography. Radiological grounds probably mean more sensitivity and include mild cases, whereas joint replacement surgery indicates severe end-stage OA. Some papers involved in the study have reported the association based on different OA definition. More and larger studies that report BMI-OA risk associations separately for OA definition are anticipated.

We found significant heterogeneity in our meta-analysis, whereas it did not reduce substantially in cohort studies and case control studies after subgroup was conducted. This may be because of the variations in OA definition, different population, diverse confounders, the irregularities of category-specific information and the way of BMI report. Begg methods considered that this test had larger test performance when the number of involved studies were more than 75, while moderate ability when 25 studies. Egger et al. used linear regression method to detect the symmetry of funnel plot, and its statistics performance was higher than Begg methods. So we used trimming and filling analysis to further evaluate publication bias. Comprehension of trimming and filling result did not lie in how many studies should be included, and the result remained similar after being adjusted by trimming and filling analysis. Influence analysis suggested that no single studies affected significantly the summary estimate.

There are some limitations considered in this study. First, smoking seems to be a major potential confounder [29]. However, we could not determine the effect of smoking because few studies were stratified by smoking status. Second, radiographic OA cases based on traditional criteria using Kellgren-Lawrence scales are generally defined. Alternative classification scales for OA have been used [11]. Studies using both the traditional Kellgren-Lawrence and newer modified individual scales might account for the variation. Third, specific occupational groups whose jobs requiring repetitious tasks show high predisposition to developing OA in repetitively used joints [25,39]. BMI, defined by anthropometric measures or self-reported, may contribute to different results. All these could be additional bias and need further research. Finally, some important confounders have not been measured with sufficient precision, or have not been measured at all in original studies. Since BMI seemed to predict slightly stronger for bilateral OA than unilateral OA [43]. The positive association of BMI with bilateral knee OA was even more obvious. Unfortunately, few studies analyzed such a differentiation [43]. We could not rule out the possibility of those potential confounders and brought about heterogeneity. In addition, anthropometric measures other than BMI, such as waist-to-hip ratio and waist circumference, also serve as better measures of adiposity. However, few studies provided such information to permit comprehensive analysis of associations across studies.

WHO endorses the use of BMI (kilogram per square meter) to define obesity as BMI $\geq 30\,kg/m^2$ and overweight as BMI $\geq 25\,kg/m^2$. Anthropometric measurement or self-reported of BMI at baseline could not represent that of changes during follow-up. If BMI is generally obtained from the baseline year, the analyses do not allow for that a large period of time have elapsed between the ascertainment of exposure and the development of outcome. However, fewer articles reported the association between BMI earlier in life and the risk of OA in the life course [58]. Moreover, the prevalence of OA increases with age, which is further aggravated by obesity. Risk estimates assessed by BMI at age 18 years were significantly greater than that by "recent" BMI. Crucial questions remain unresolved about the cumulative effect of excess bodyweight over several decades, the effect of key weight-change periods in the life course of individuals, and interactions with other potential risk factors.

Although with some limitations, our meta-analysis provides an obvious evidence of dose-response relationship as a continuous scale for the association between increased BMI with the risk of developing knee OA. We have transformed category-specific risk estimates into a quantitative risk estimate associated with every $5\,kg/m^2$ increase in BMI. Most importantly, we have modeled a $5\,kg/m^2$ increase in BMI, and the result may be considerably practical and theoretically important. Obesity is particularly important for developing OA in weight-bearing joints, and modifying obesity can prevent osteoarthritis-related pain and disability. The finding further supports the significance of obesity in the etiology of osteoarthritis. The prevention of obesity is important, as it has adverse effects on health. Also, change of body weight is useful and feasible.

Disclosure of interests

The authors declare that they have no conflicts of interest concerning this article.

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